Matching Medicines to Genetic Makeup in Oncology

Dr Howard L McLeod

Professor of Pharmacy & Medicine

Director, Institute for Pharmacogenomics and Individualized Therapy

University of North Carolina, Chapel Hill, USA

UNC N.C. CANCER HOSPITAL
LINEBERGER COMPREHENSIVE CANCER CENTER

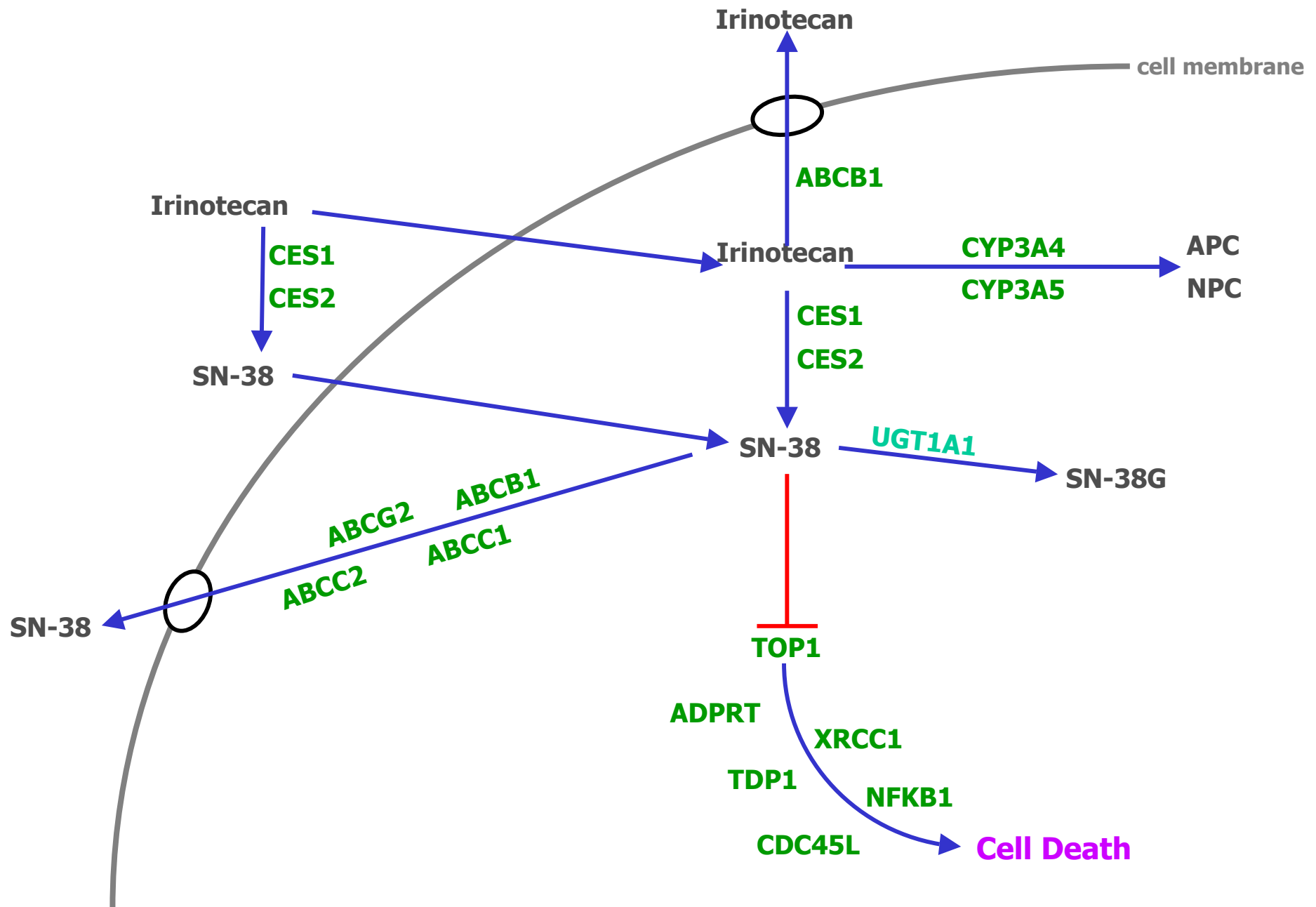UNC INSTITUTE FOR PHARMACOGENOMICS AND INDIVIDUALIZED THERAPY

The clinical problem

- Multiple active regimens for the treatment of most diseases
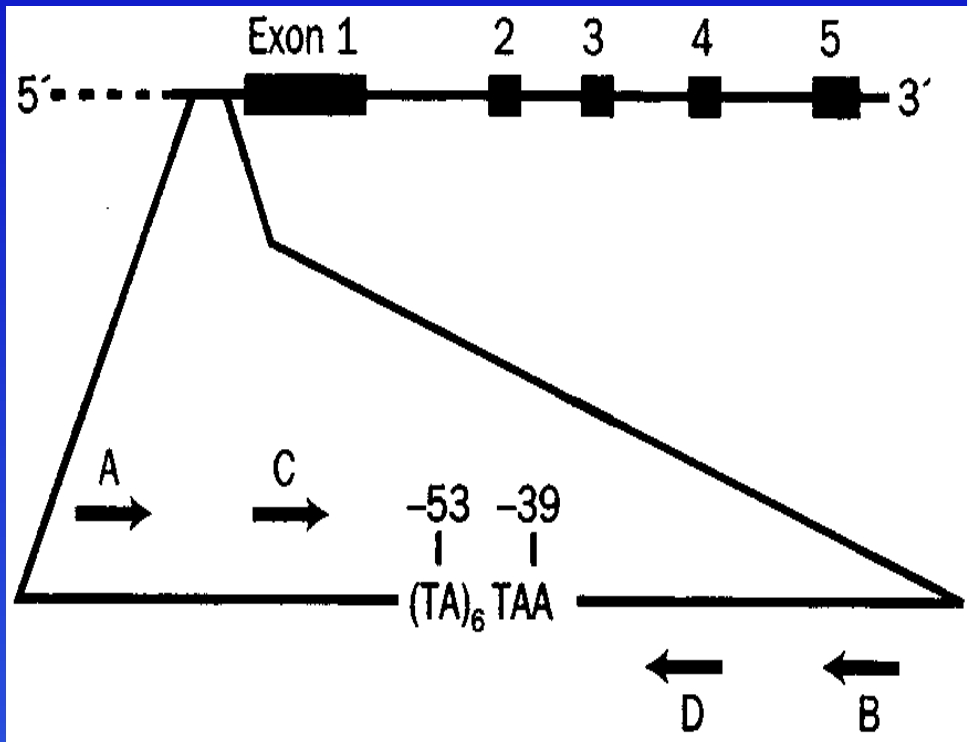- Variation in response to therapy
- Unpredictable toxicity
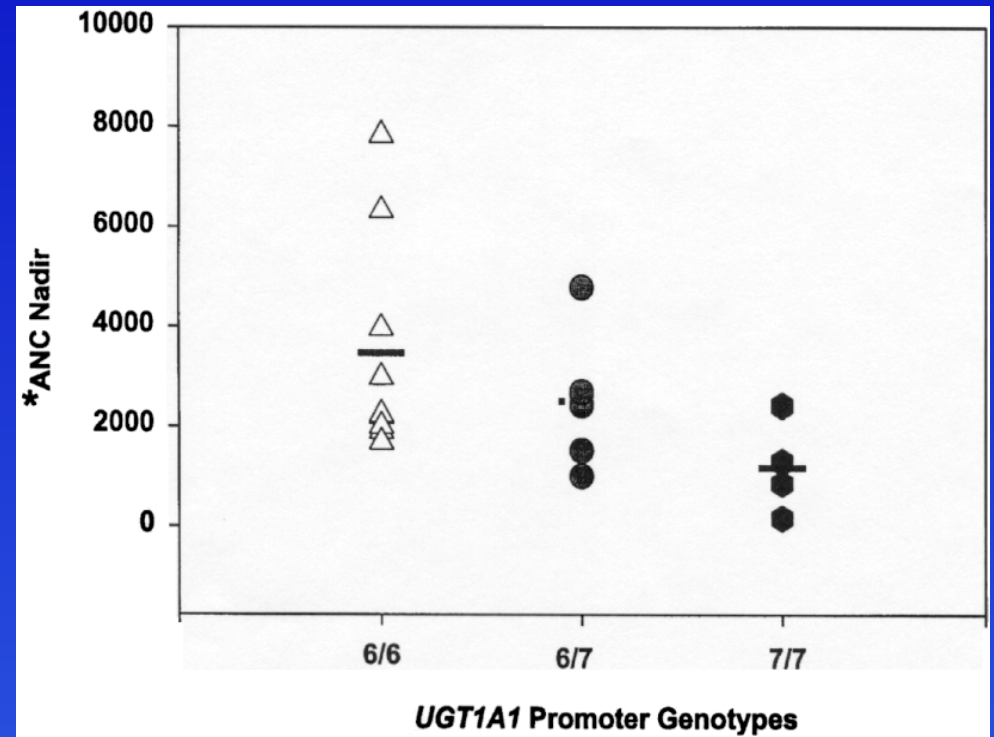
$$$$$$$$$$$$$

With choice comes decision

Irinotecan Pathway

UGT1A1: Promoter Polymorphism and Toxicity

UGT1A1 gene structure

Iyer et al. 2002

Severe Neutropenia Risk with Irinotecan Use: UGT1A1 7/7 vs 6/6 + 6/7 Genotypes Unadjusted Odds Ratio

Author	n/N (%)		Est. Odds Ratio	95% CI
	7/7	6/6 + 6/7		
Innocenti	3/6 (50%)	3/53 (6%)	16.7	2.3 - 120.6
Rouits	4/7 (57%)	10/66 (15%)	7.5	1.4 - 38.5
Marcuello[a]	4/10 (40%)	18/85 (21%)	2.5	0.6 - 9.7
Ando[b]	4/7 (57%)	22/111 (20%)	5.4	1.1 - 25.9

[a]Gr 3+ neutropenia.
[b]Gr 4 leukopenia and/or Gr 3+ diarrhea.

Revised Irinotecan (Camptosar®) Label

population is homozygous for the UGT1A1*28 allele. In a prospective study, in which irinotecan was administered as a single-agent on a once-every-3-week schedule, patients

Patients with Reduced UGT1A1 Activity

Individuals who are homozygous for the UGT1A1*28 allele are at increased risk for neutropenia following initiation of CAMPTOSAR treatment. A reduced initial dose should be considered for patients known to be homozygous for the UGT1A1*28 allele (see DOSAGE AND ADMINISTRATION). Heterozygous patients (carriers of one variant allele and one wild-type allele which results in intermediate UGT1A1 activity) may be at increased risk for neutropenia; however, clinical results have been variable and such patients have been shown to tolerate normal starting doses.

A reduction in the starting dose by at least one level of CAMPTOSAR should be considered for patients known to be homozygous for the UGT1A1*28 allele (See CLINICAL PHARMACOLOGY and WARNINGS). The appropriate dose reduction in this patient population is not known.

Summary of 10 Pharmacogenetic Trials

Irinotecan dose (mg/m^2)	Schedule (No. of days bet/ doses)	Concomitant chemotherapy	Rate of Grade 3/4 hematological toxicity		Trial
			7/7	6/6 & 6/7	
350	21	None	83% (5/6)	11% (6/55)	Innocenti 2004
300	21	None	50% (2/4)	0% (0/16)	Iyer 2002
200	21	Oxaliplatin	55% (6/11)	12% (11/92)	McLeod 2006
180	14	5-Fluorouracil	60% (3/5)	22% (11/51)	Marcuello 2004
180	14	None	57% (4/7)	24% (12/51)	Chiara 2005
180	14	5-Fluorouracil	60% (3/5)	29% (12/41)	Rouits 2004
180	14	5-Fluorouracil	18% (4/22)	14% (33/228)	Toffoli 2006
100	7	5-Fluorouracil	18% (2/11)	9% (9/98)	McLeod 2006
80	7	Raltitrexed	14% (1/7)	6% (3/49)	Massacesi 2006
100, 125	7	Capecitabine	0% (0/6)	5% (3/56)	Carlini 2005

Dose Modulates Association Between *UGT1A1*28/*28* and Hematological Toxicity
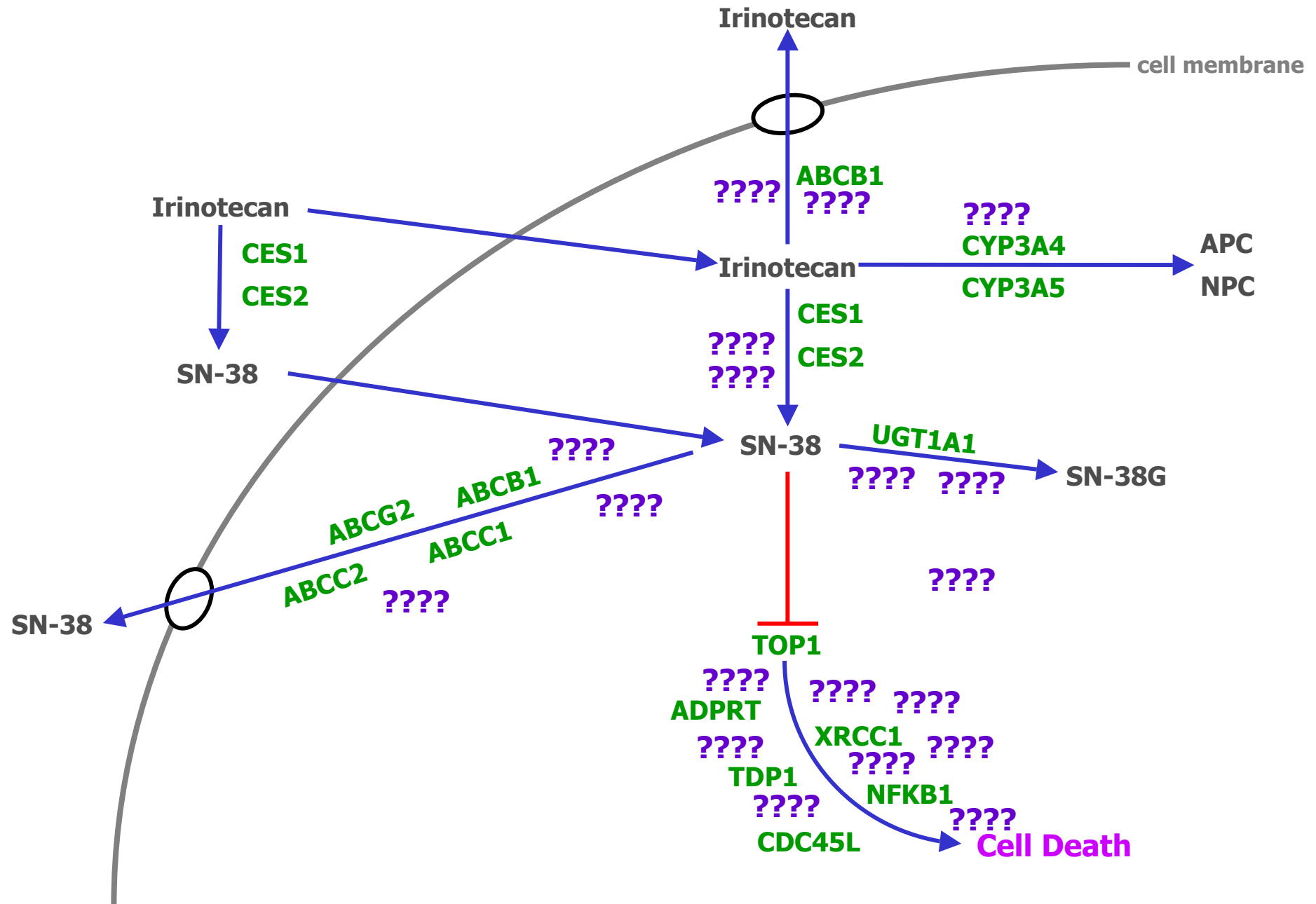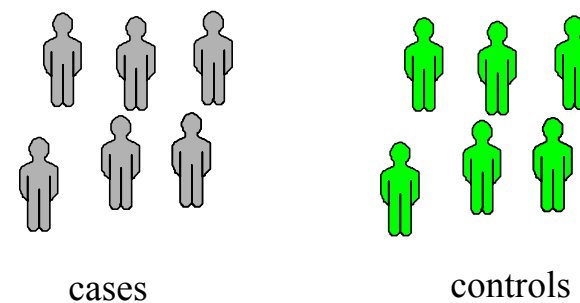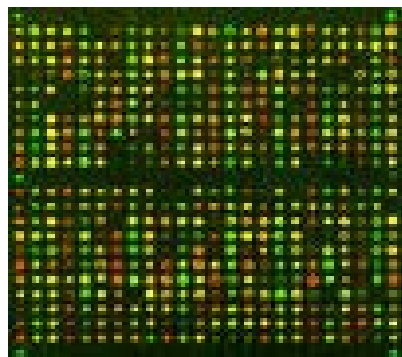
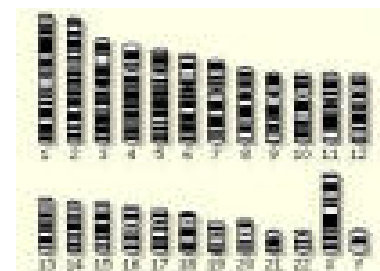Dose (continuous): generalized linear mixed model

Hoskins et al. *J Natl Cancer Inst.* 2007. 99:1290.
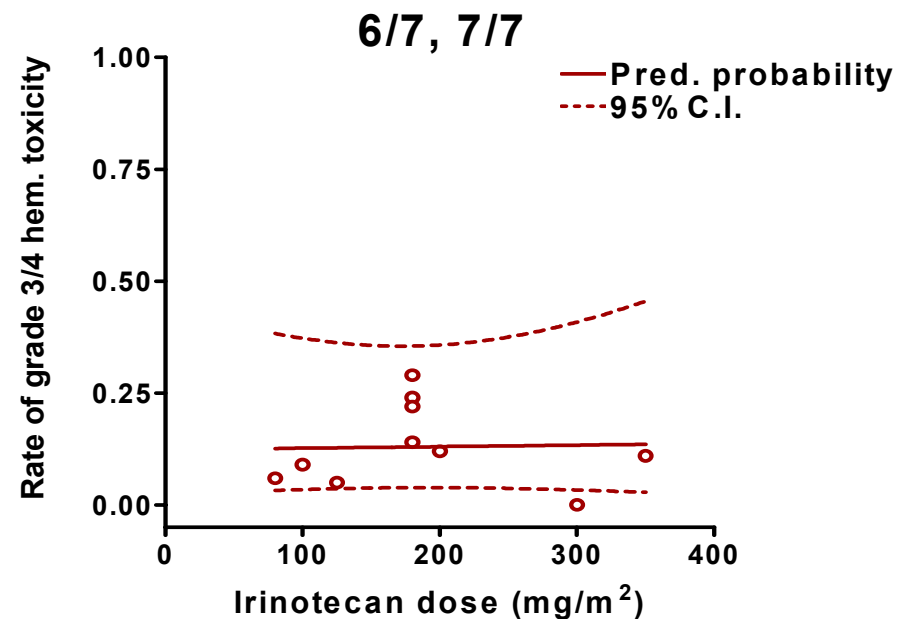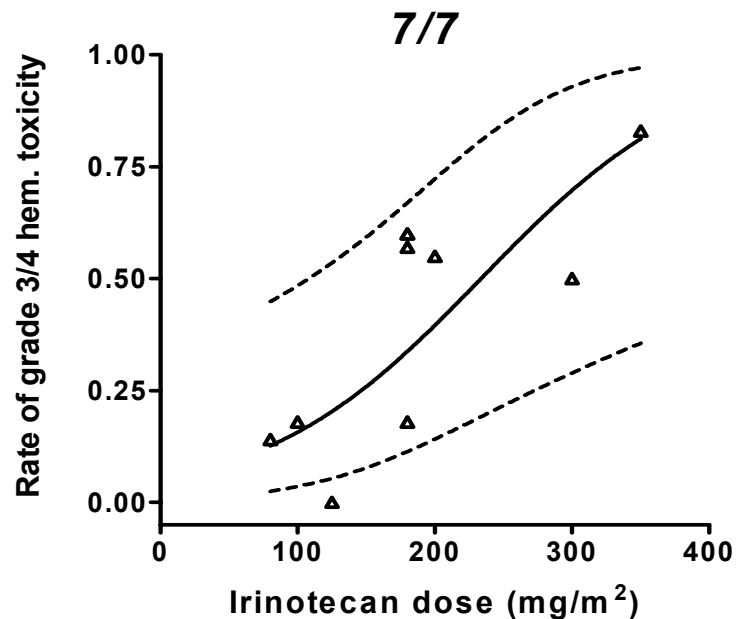
Dose Modulates Association Between *UGT1A1*28/*28* and Hematological Toxicity

Dose (categorical): generalized linear mixed model (7/7 versus 6/6, 6/7)

Irinotecan dose	Odds ratio (95% C.I.)	*P*
<150 mg/m^2	1.80 (0.37-8.84)	0.41
150-250 mg/m^2	3.23 (1.52-6.81)	0.008
>250 mg/m^2	27.8 (3.97-195)	0.005

Hoskins et al. *J Natl Cancer Inst*. 2007;99:1290.

We do not know very much about drugs

Grade

DBA/2J CBA/J PL/J AKR/J NOD/LtJ BALB/2J SWR/J C57L/J RIIIS/J NZB/B1NJ A/J

Model systems

HapMap

Linkage

Discovery Strategies

Expression array

cases   controls
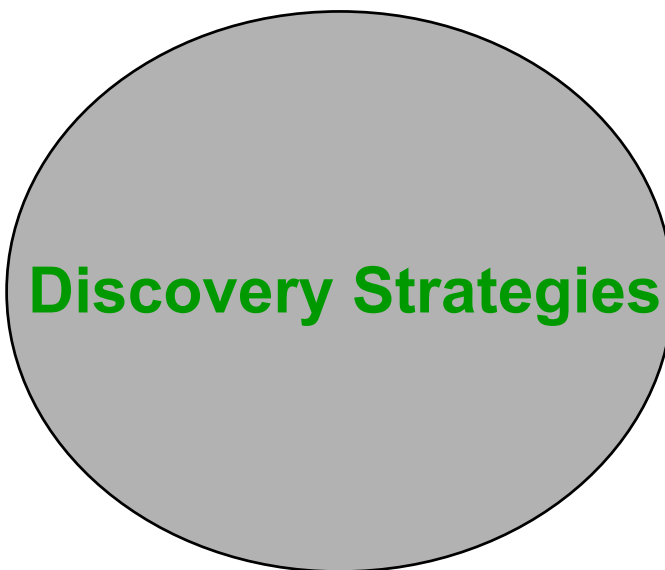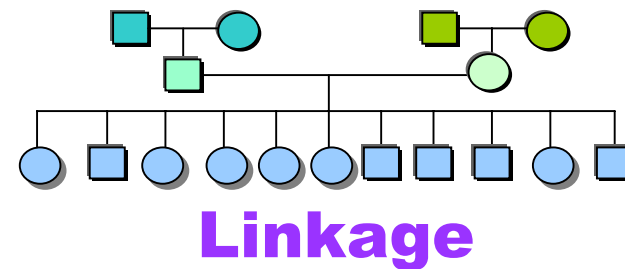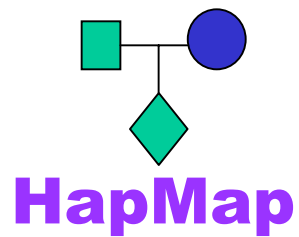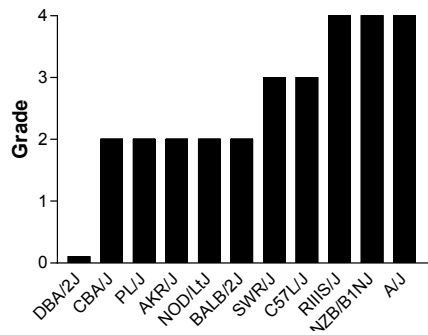
Association

What needs to be done to determine hope vs hype?

- Find the 'right' biomarkers

- Validate in robust datasets

- Apply them!

Correlative science: business as usual

Phase I   Phase II   Phase III

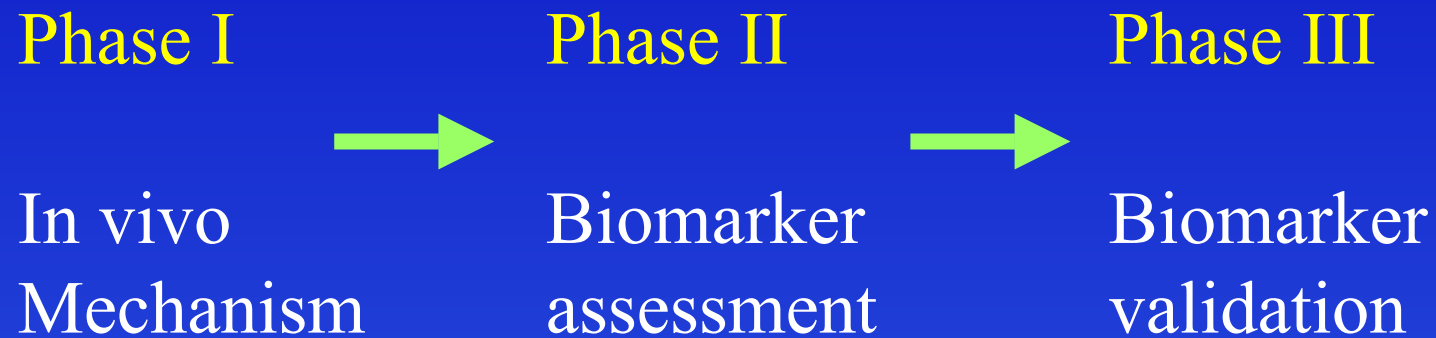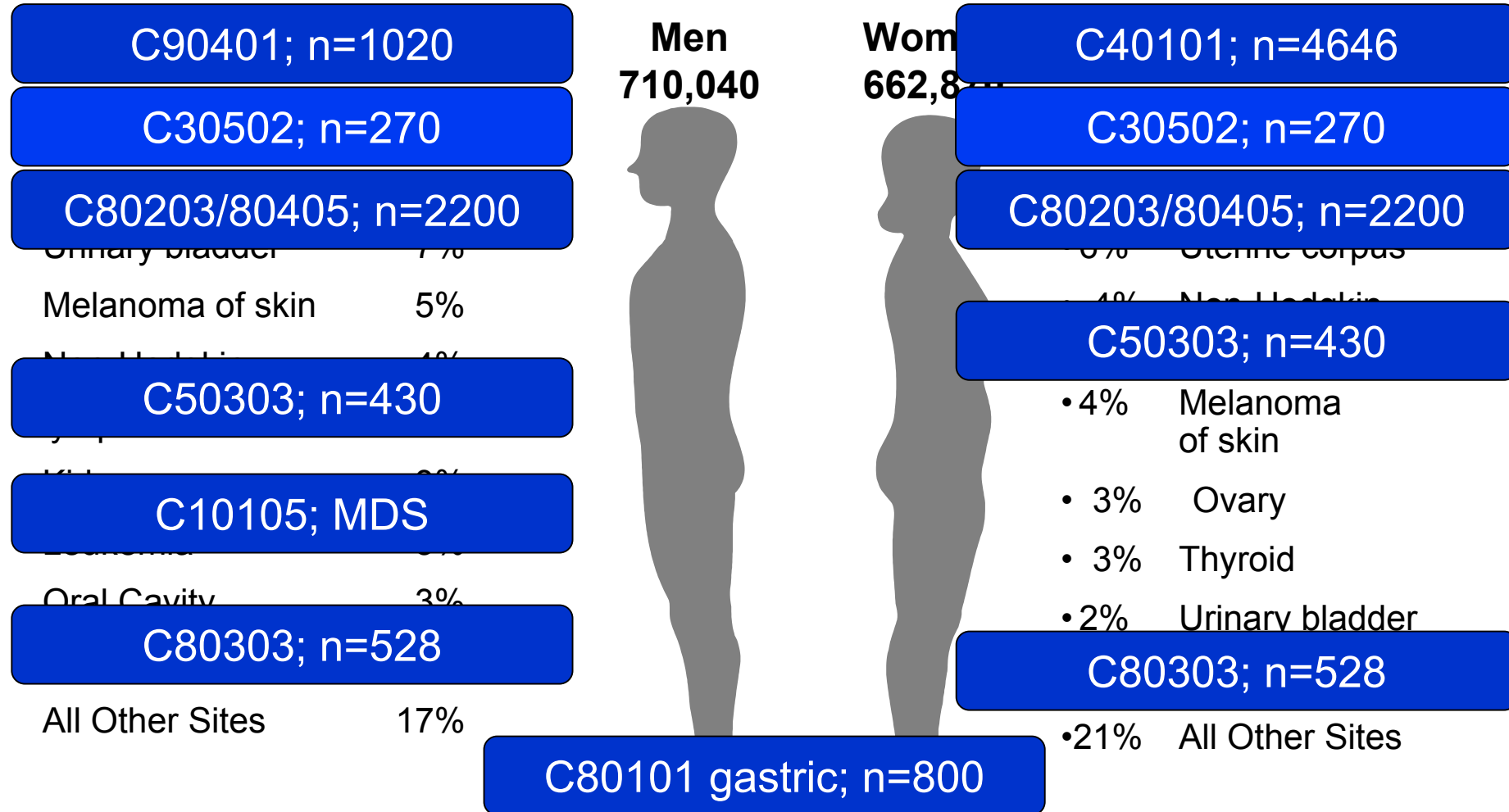In vivo   Biomarker   Biomarker
Mechanism   assessment   validation

2008 Estimated US Cancer Cases*

Men
710,040

Wom **662,8...**

C90401; n=1020

C30502; n=270

C80203/80405; n=2200

Urinary bladder   7%

Melanoma of skin   5%

C50303; n=430

C10105; MDS

Oral Cavity   3%

C80303; n=528

All Other Sites   17%

C40101; n=4646

C30502; n=270

C80203/80405; n=2200

Uterine corpus

Non-Hodgkin

C50303; n=430

- 4%   Melanoma of skin
- 3%   Ovary
- 3%   Thyroid
- 2%   Urinary bladder

C80303; n=528

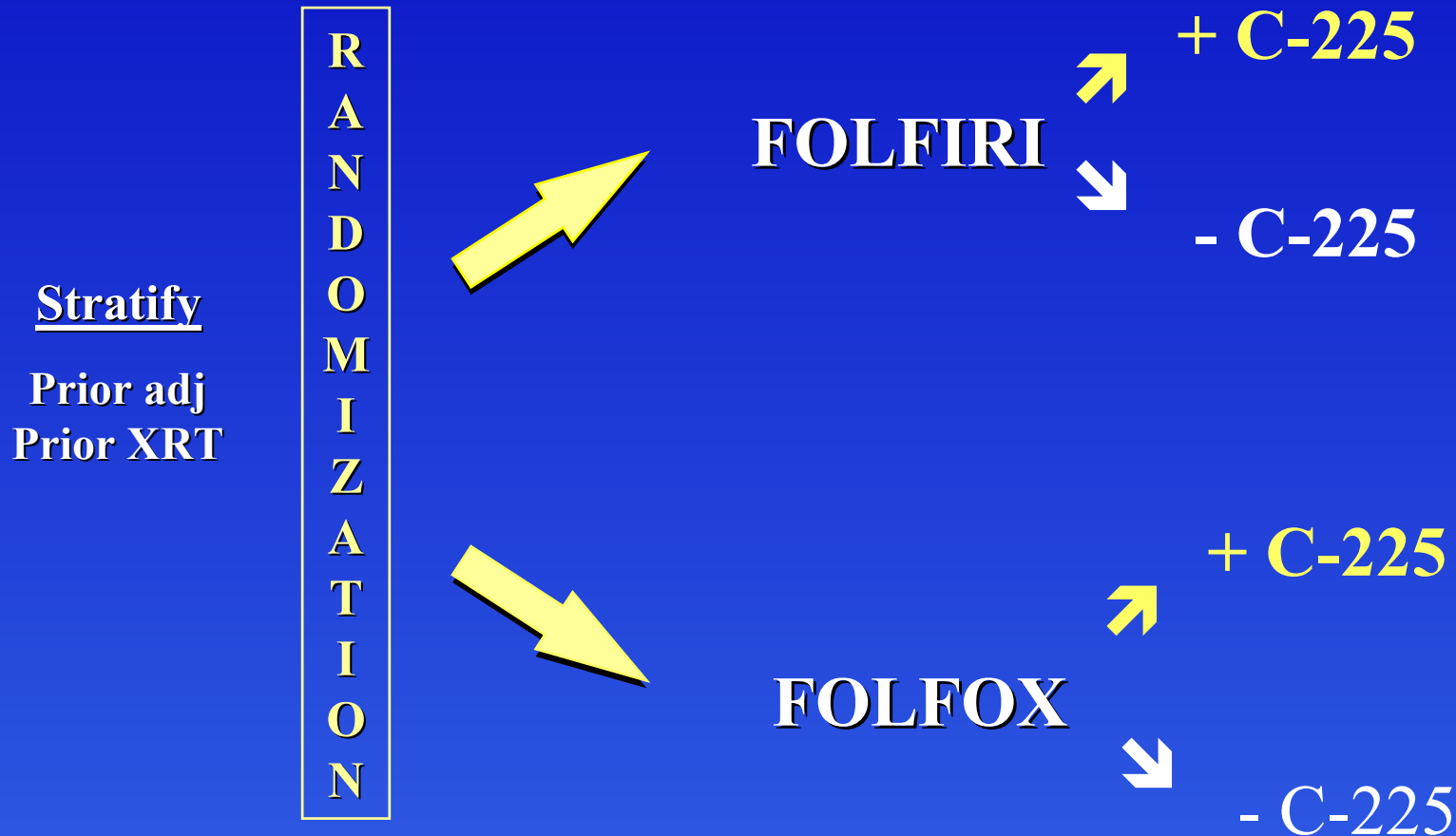- 21%   All Other Sites

C80101 gastric; n=800

*Excludes basal and squamous cell skin cancers and in situ carcinomas except urinary bladder.
Source: American Cancer Society, 2005.

Closed				
80203	Venook	Ph III CPT-11/5-FU/Leu or Ox/5-FU/Leu +/- C225 in colorectal ca	60304/McLeod/PG	185
80303	Kindler	Ph III pancreatic ca	60401/Innocenti/PG	396

5-Fluorouracil
TYMS
MTHFR

Oxaliplatin
ERCC1
ERCC2
GSTP1
- ✔ SLC transporters

Irinotecan
- ✔ UGT1A7
- ✔ UGT1A1
- ✔ ABCC2
- ✔ ABCC4
- ✔ SLCO1B1

Cetuximab
EGFR
FCGRII and III
Other clearance genes

NIH Pharmacogenetics Research Network

SPONSORS:

NIGMS
NHLBI NHGRI
NCI
NIEHS
NLM

<u>Research Sites</u>:

Brigham and Women's Hosp.

Children's Hosp. Oakland

Indiana Univ.

Mayo Foundation

Stanford Univ.

UCSF X 2

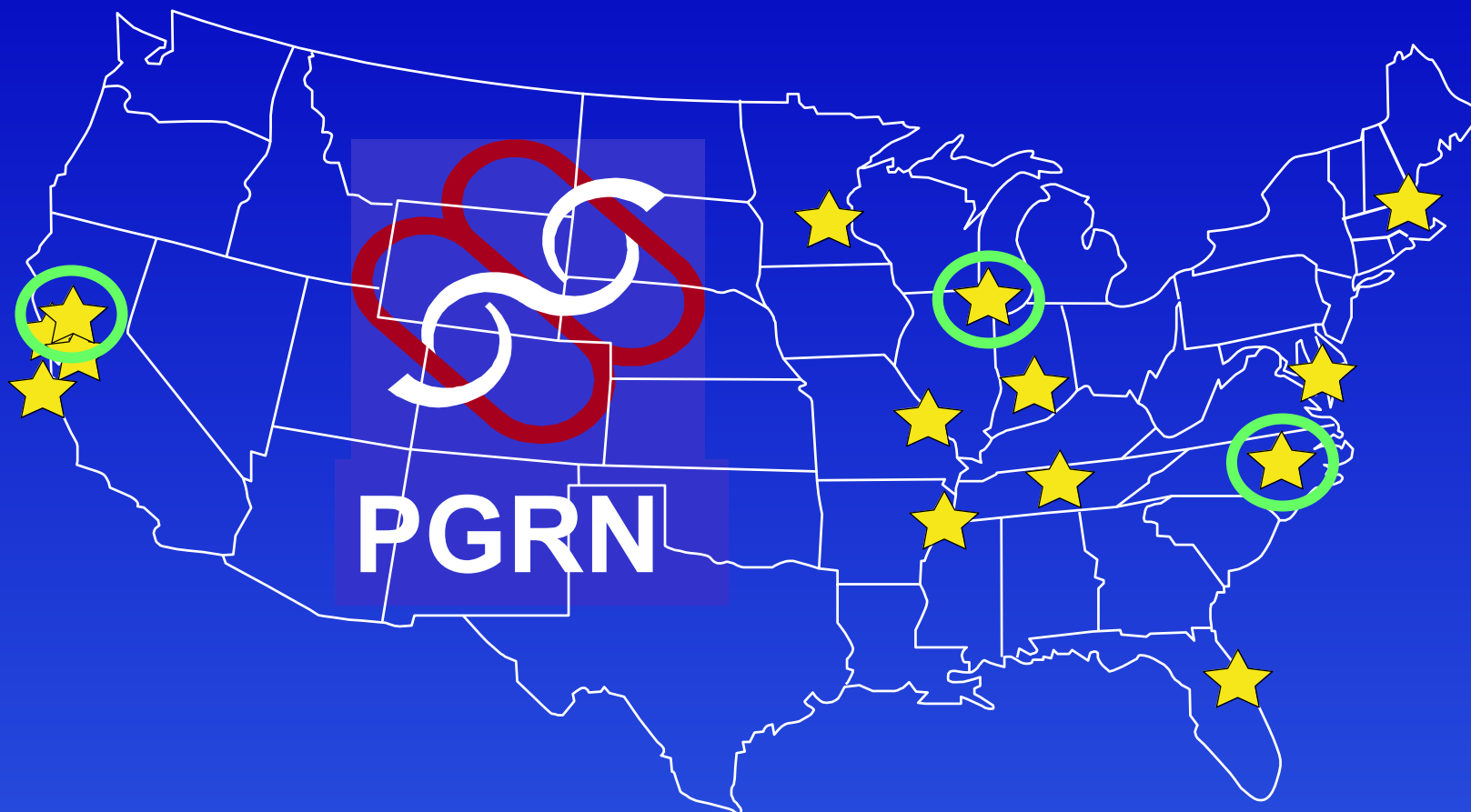Univ. of Chicago

Univ of Florida

Univ of Maryland

Univ of N Carolina

Vanderbilt Univ.

Washington Univ.

PGRN

www.nigms.nih.gov/pharmacogenetics

www.pharmgkb.org

PharmGKB
The Pharmacogenetics and Pharmacogenomics Knowledge Base

Genotyping was performed for the cellular transporters ABCC2, ABCC4, ABCG2, SLCO1B1, SLC22A1, and SLC22A2 and the UGT1A1*6, *28 and UGT1A7 genotypes.

ABCG2 34G>A was associated with relative susceptibility to FOLFOX and resistance to FOLFIRI ($p < 0.013$, Caucasians only).

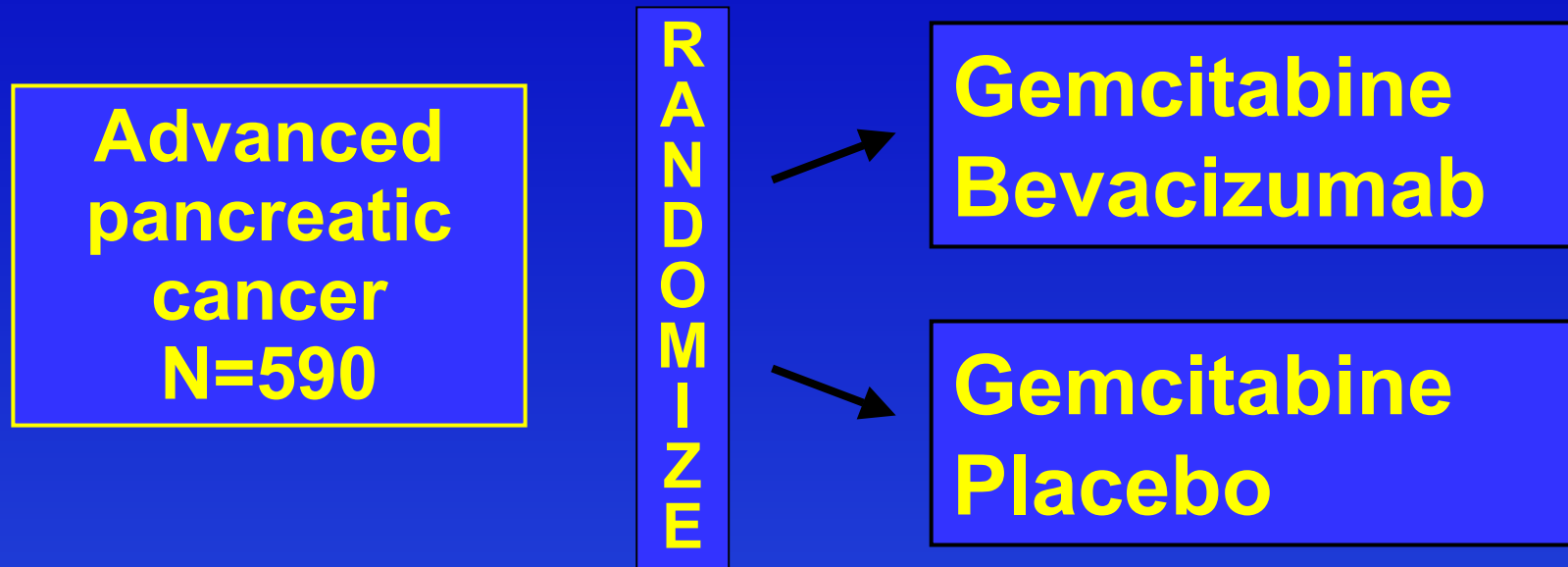|	ABCG2 34G/G	ABCG2 34A/G
FOLFOX	37/65 (57%)	5/5 (100%)
FOLFIRI	32/73 (44%)	1/5 (20%)

Genome wide association study in pancreatic cancer patients treated with chemotherapy

CALGB #80303

Federico Innocenti, MD, PhD
Nancy Cox, PhD

UofC(PGRN)/Riken/CALGB

CALGB 80303 Trial design

Advanced pancreatic cancer N=590

RANDOMIZE

→ **Gemcitabine Bevacizumab**

→ **Gemcitabine Placebo**

Stratification:
- Performance status: 0/1 vs. 2
- Extent of disease: metastatic vs. locally advanced
- Prior radiation: yes/no

Kindler et al, *Proc ASCO, 2007*

CALGB 80303: Treatment

R A N D O M I Z A T I O N

Gemcitabine 1000 mg/m^2 D 1, 8, 15
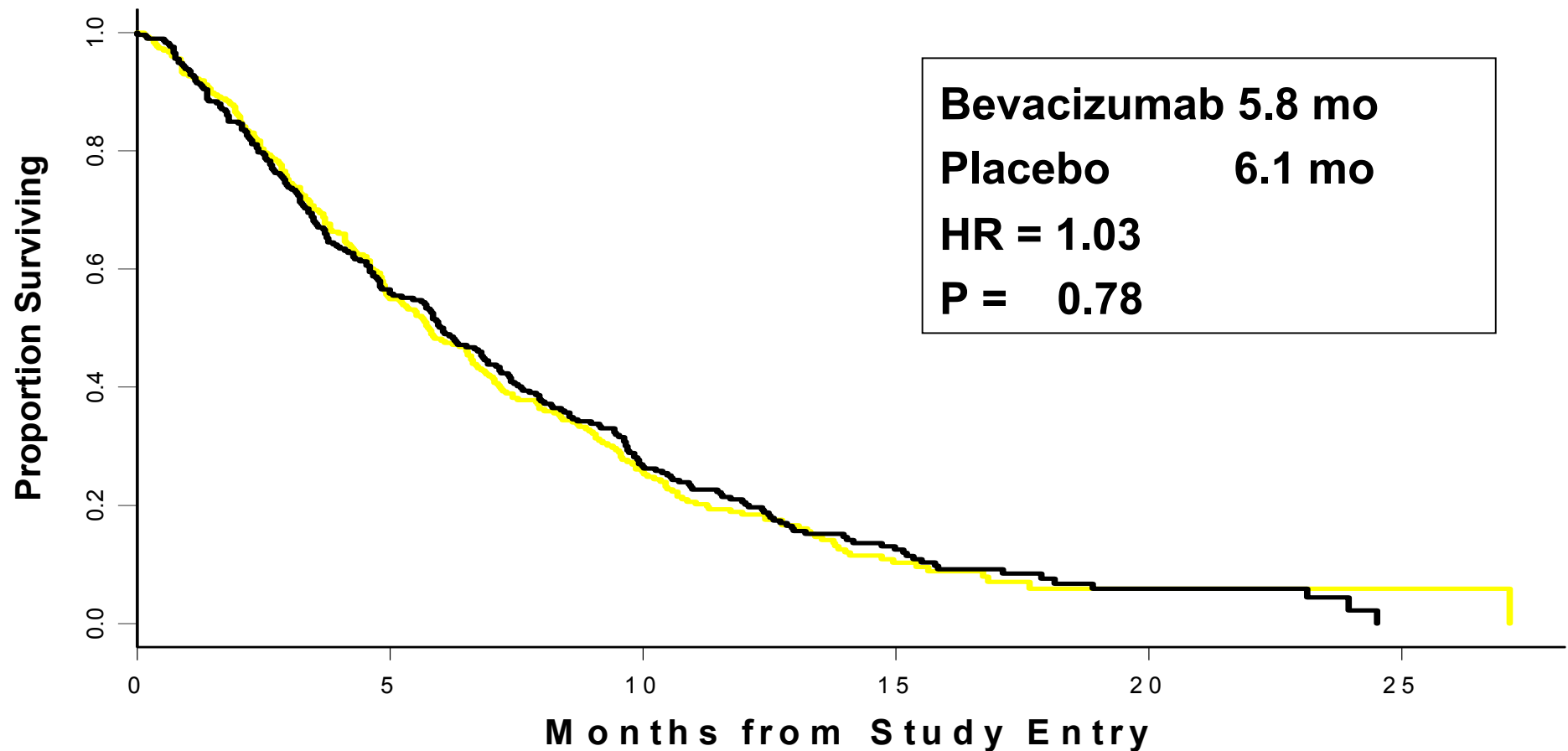**Bevacizumab** 10 mg/kg D 1, 15

Gemcitabine 1000 mg/m² D 1, 8, 15
Placebo D 1, 15

1 cycle = 28 days
CT scans: obtained every 2 cycles

CALGB 80303:
Overall Survival by Treatment Arm

Toxicity

	GP (n=183)	GB (n=191)
G3-4 Neutropenia	31%	34%
G3-4 Hypertension	2%	10%
G2-4 Hypertension	5%	16%
G3-4 Proteinuria	1%	5%
G2-4 Proteinuria	6%	13%

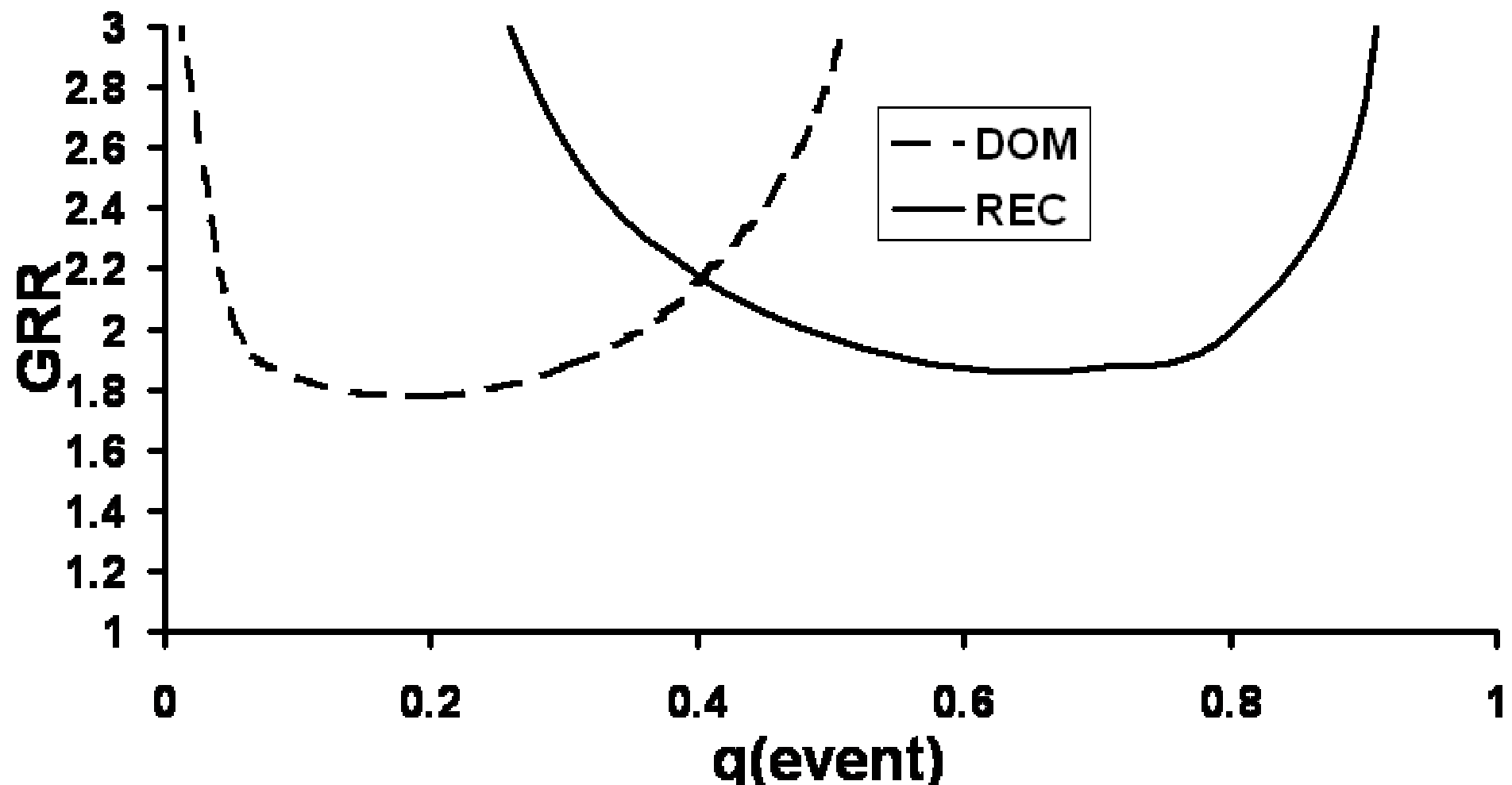# Objectives

- **To identify genetic variation associated with differences in toxicity and efficacy**

- **Primary**
  - **Severe myelosuppression (G3-4 neutropenia)**

- **Secondary**
  - **G2-4 hypertension and proteinuria**

  - **Overall survival**

Platform

- **Illumina's HumanHap550 Genotyping BeadChip**

- **QC – preliminary QC was outstanding**

GRR vs. q; 80% power, p<.001; 33% trait

Results
Genotyping

- **Very little missing data**
- **Very few departing data from HWE**
- **No apparent plate effects**

- **A couple of duplicated and some contaminated samples**
- **Sex misclassification: solved**
- **Discrepancy between the phenotype and the genotype data sets**

Results

- **355 samples**
- **Europeans**
- **Neutropenia and hypertension in both arms, combined**

- **Several genes not yet annotated**
- **Several proteins with little information on function**
- **Intronic variants**

Coverage of 10 candidate genes in the 550 chip

Gene	SNPs 550	tSNPs HapMap	tSNPs resequencing
VEGF, chr 6: 13.4 Kb	4	7	16
FLT1, chr13: 193.4 Kb	40	53	-
KDR, chr4: 47.1 Kb	12	22	14
CDA cytidine deaminase, chr1: 29.9 Kb	8	14	-
DCK deoxycytidine kinase, chr4: 37.2 Kb	2	2	-
DCTD dCMP deaminase, chr4: 27.4 Kb	17	20	-
SLC29A1, chr6: 14.6 Kb	3	5	-
SLC29A2, chr11: 9.3 Kb	1	1	-
SLC28A1, chr15: 61.1 Kb	45	48	-

Conclusions

- **A very worthwhile experiment**
  - **feasibility**

- **The vast majority of gene candidates are not previously identified candidates**

- **The vast majority of SNPs have no established function**

- **New leads**
- **Function to be established**

Open				samples
20501	Baer	Multidrug Resistance Protein Gene Polymorphism in AML	PET#-N/A. Tissue Bank/PG	500?
10105	Gupta	PTK787 in MDS	60303/PK/Miller and 60404/PG/McLeod	154
40101	Shulman	CA vs Taxol in node	60202/Kroetz/PG	1925
50303	Wilson	RCHOP vs EPOCH-R in B-cell lymphoma	60405/McLeod/PG	100
80101	Fuchs	Adj chemo after resect	60201/McLeod/PG	272
80403	Enzinger	ECF-C vs IC-C vs FOLFOX-C in mets colorectal ca	60601/Innocenti/PG	61
80405	Venook	FOLFOX/FOLFIRI + bv, + C225, or + bv/C225 for mets colon ca	60501/McLeod/PG	719
90401*	Kelly	Est/doc vs Est/doc/bev for HRPC	60404/TBD/PG	835

In Development			
30607	Socinski	NSCLS of chemo +/- sunitinib	60702/TBD/PG
30702	Ready	Genome-guided Chemotherapy for Untreated and treated Advanced Stage NSCLC	Maitland/PG
30801	Edelman	Selective COX-2 Inhibition in COX-2 Overexpressing Advanced NSCLC	Maitland/PG
40502	Rugo	Rand wkly taxol or nab-taxol +/- bevaciz met br ca	Kroetz/Dees/PG
40503	Dickler	Endoc tx vs endo tx + bev for postmeno wm w/ recpetor + adv br ca	60605/Innocenti
40601	Carey	Rand neoadj chemo +/- carbo + trastuz and/or lapat HER2+ br ca	60701/Dees & Kroetz/PG
40603	Sikov	Ph II Neoadjuvant ACT +/- bev and +/- carboplatin	60703/Kroetz/PG
90601	Rosenberg	Ph III of gem/cis vs. gem/cis + bev for TCC	60707/McLeod/PG
80702	Meyerhardt	celecoxib and vitamin D as adjuvant therapy for stage III colon cancer	?
80801	Saab	phase II axitinib +/- cape in refractory pts with met pancreas cancer	McLeod/PG
80802	Abou-Alfa	sorafenib plus doxorubicin versus sorafenib in patients with advanced hepatocellular carcinoma (HCC)	Innocenti/PG
70604	Khatcheressian	Standard versus longer dosing of zoledronic acid in metastatic cancer	?/PG

What needs to be done to determine hope vs hype?

- Find the 'right' biomarkers

- Validate in robust datasets

- Apply them!

NIH Pharmacogenetics Research Network

PGRN

www.nigms.nih.gov/pharmacogenetics   **www.pharmgkb.org**

PharmGKB
The Pharmacogenetics and Pharmacogenomics Knowledge Base